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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/538,912	06/13/2005	Tatsuya Ohashi	050381	9528

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EXAMINER
GRUN, JAMES LESLIE

ART UNIT	PAPER NUMBER
1641	

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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/538,912	OHASHI, TATSUYA	
	Examiner	Art Unit	
	James L. Grun	1641	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *05 November 2007*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-16* is/are pending in the application.

4a) Of the above claim(s) *12* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-11 and 13-16* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☒ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *6/13/05;8/1/07*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

Applicant's election of Group I, claims 1-11 and 13-16, in paper filed 05 November 2007 is acknowledged. Because applicant did not distinctly and specifically point out the supposed errors in the restriction requirement, the election has been treated as an election without traverse (MPEP § 818.03(a)). Claim 12 is withdrawn from further consideration pursuant to 37 CFR 1.142(b) as being drawn to a nonelected invention.

The following is a quotation of the first paragraph of 35 U.S.C. § 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

The specification is objected to under 35 U.S.C. § 112, first paragraph, as failing to provide an adequate written description of the invention, and failing to adequately teach how to make and/or use the invention, i.e. failing to provide an enabling disclosure.

Claims 1-11 and 13-16 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while possible of being enabling for the Trk49 and Trk62 antibodies, does not reasonably provide enablement for the scope of antibodies as claimed or even for other antibodies specific for the 5a and 5b isoforms of tartrate resistant acid phosphatase. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims.

Many parameters of a detection immunoassay need to be defined before it can be predictably practiced to perform the desired detection of a given target substance in the presence

of a given competitor. Chief among these are the definition of the target/competitor pairs and appropriate specific antibodies which function for selective binding of the target substance and/or competitor. Applicant does not teach or suggest target substance/competitive substance pairs, or antibodies selective therefor, other than the 5a and 5b isoforms of tartrate resistant acid phosphatase and fragments thereof. Unpredictable experimentation to define target/competitor pairs and appropriate specific antibodies which function for selective binding of the target substance and/or competitor, unguided by applicant's disclosure, would be required for one to predictably practice the invention with other than the 5a and 5b isoforms of tartrate resistant acid phosphatase and fragments thereof. Even for the exemplified detection of the isoforms of tartrate resistant acid phosphatase and their fragments, applicant provides no adequate description and guidance for the preparation of detection reagents which function in the invention other than the Trk49 and Trk62 antibodies. In this regard, the reference of Janckila et al. (Hybridoma 16: 175, 1997) teaches the difficulties in eliciting monoclonal antibodies to the isoforms of tartrate resistant acid phosphatase (see e.g. page 179). Absent further guidance from applicant, one would not be assured of the ability to predictably practice the method as claimed with other target/competitor pairs or even with other than the Trk49 and Trk62 antibodies because one would have no assurance of predictably obtaining relevant reagents having the relevant immunological properties which function in the invention. Note that an enabling disclosure for the preparation and use of only a few analogs of a product does not enable all possible analogs where the characteristics of the analogs are unpredictable. Amgen Inc. v. Chugai Pharmaceutical Co. Ltd. (18 USPQ 2d 1027 (CAFC 1991)).

Claims 1-11 and 13-16 are further rejected under 35 U.S.C. § 112, first paragraph, as failing to provide an adequate written description of the invention and failing to provide an enabling disclosure, because the specification does not provide evidence that the required biological materials are: (1) known and readily available to the public; (2) reproducible from the written description; or, (3) deposited in compliance with the criteria set forth in 37 CFR §§ 1.801-1.809.

It is unclear if cell lines which produce antibodies having the exact chemical identity and properties of the antibodies designated Trk49 and Trk62 are known and publicly available, or can be reproducibly isolated without undue experimentation. Accordingly, filing of evidence of the reproducible production of the cell lines and antibodies necessary to practice the instant invention or filing of evidence of deposit is required. Without a publicly available deposit of the above cell lines, one of skill in the art could not be assured of the ability to practice the invention as claimed. Exact replication of: the required cell line; the cell lines which produce the chemically and functionally distinct antibodies required; and/or, the required antibody's amino acid or nucleic acid sequence is an unpredictable event. For example, very different V_H chains can combine with the same V_L chain to produce antibody binding sites with nearly the same size, shape, antigen specificity, and affinity. A similar phenomenon can also occur when different V_H sequences combine with different V_L sequences to produce antibodies with very similar properties. These observations indicate that divergent variable region sequences, both in and out of complementarity-determining regions, can be folded to form similar binding site contours, which result in similar immunochemical characteristics. Therefore, it would require undue experimentation to reproduce the required monoclonal antibody species chemically as produced

by the hybridomas designated as Trk49 and Trk62. A suitable deposit of the hybridomas would satisfy the enablement requirements of 35 U.S.C. § 112, first paragraph. See the criteria set forth in 37 CFR §§ 1.801-1.809.

If the deposits are made under the terms of the Budapest Treaty, then an affidavit or declaration by Applicant, or a statement by an attorney of record over his or her signature and registration number, stating that the specific biological materials have been deposited under the Budapest Treaty, that the biological materials will be irrevocably and without restriction or condition released to the public upon the issuance of a patent and that the biological materials will be replaced should they ever become non-viable, would satisfy the deposit requirement made herein.

If the deposits have not been made under the Budapest Treaty, then in order to certify that the deposits meet the criteria set forth in 37 CFR §§ 1.801-1.809, applicant may provide assurance of compliance by an affidavit or declaration, or by a statement by an attorney of record over his or her signature and registration number, showing that:

(a) during the pendency of this application, access to the invention will be afforded to the Commissioner upon request;
(b) all restrictions upon availability to the public will be irrevocably removed upon granting of the patent;
(c) the deposits will be maintained in a public depository for a period of 30 years or 5 years after the last request or for the effective life of the patent, whichever is longer;
(d) the deposits were viable at the time of deposit; and,
(e) the deposits will be replaced if they should ever become non-viable.

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 1-11 and 13-16 are rejected under 35 U.S.C. § 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claims 1-8 and 13-16 are method claims and, as such, they should clearly set forth the various method steps in a positive, sequential manner using active tense verbs such as mixing, reacting, and detecting. Method steps involving "employing" or "using" are not valid method steps. In these claims, "the use" and "the level" lack antecedent basis.

Claims 2-8 and 13-16 should recite --The-- immunoassay method for proper reference to the previously recited claim components.

In claim 3 and claims dependent thereupon, "the enzymatic activity" lacks antecedent basis.

In claim 8, the interrelationships of the components are not clear because it is not clear that "dissolved" further limits "adsorbed on a carrier" as previously recited.

In claims 9-11, "the use" lacks antecedent basis.

Claims 10 and 11 should recite --The-- kit for proper reference to the previously recited claim components.

In claim 11, the interrelationships of the components are not clear because it is not clear that "dissolved" further limits "adsorbed on a carrier" as previously recited.

The following is a quotation of the appropriate paragraphs of 35 U.S.C. § 102 that form the basis for the rejections under this section made in this Office action:

A person shall be entitled to a patent unless --

(b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

(e) the invention was described in-
(1) an application for patent, published under section 122(b), by another filed in the United States before the invention by the applicant for patent or
(2) a patent granted on an application for patent by another filed in the United States before the invention by the applicant for patent,
except that an international application filed under the treaty defined in section 351(a) shall have the effects for the purposes of this subsection of an application filed in the United States only if the international application designated the United States and was published under Article 21(2) of such treaty in the English language;

Claims 1, 2, and 7-11 are rejected under 35 U.S.C. § 102(b) as being clearly anticipated by Furie et al. (US 4,769,320).

Furie et al. provided two antibodies, with specificity and selectivity for each of an abnormal human prothrombin with reduced enzymatic activity and native human prothrombin, for immunoassay of the two forms of prothrombin present in the same sample. The affinities of the two antibodies for the two prothrombin forms are taught (see e.g. Figs. I and II). Immunoassay formats with the antibodies immobilized on a solid phase are taught (see e.g. col. 28).

The following is a quotation of the appropriate paragraphs of 35 U.S.C. § 103 which forms the basis for all obviousness rejections set forth in this Office action:

(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.
(c) Subject matter developed by another person, which qualifies as prior art only under one or more subsections (e), (f) and (g) of section 102 of this title, shall not preclude patentability under this section where the subject matter and the claimed invention were, at the time the invention was made, owned by the same person or subject to an obligation of assignment to the same person.

Claims 1, 2, and 7-11 are rejected under 35 U.S.C. § 102(b) as anticipated by or, in the alternative, under 35 U.S.C. § 103(a) as obvious over Davalian et al. (US 6,190,873).

Davalian et al. teach immunoassays for cyclosporin, including the use of a variety of supports (see e.g. cols 13-14) and labels (see e.g. cols. 14-15) in a variety of immunoassay formats involving specific binding pair members immobilized on a solid support (see e.g. cols. 26-30). In addition to antibodies specific for cyclosporin, antibodies binding to a cross-reactive material, such as a cyclosporin metabolite, which interferes with the assay for cyclosporin are included to prevent the interference (see e.g. cols. 31-32, 34-35, and 49-55). However, the relative affinities of the two antibodies for the two materials, cyclosporin and cyclosporin metabolite, cannot be determined from the reference. Inherently the antibodies had the relative affinities as instantly claimed, or, in the alternative, it would have been obvious to have provided antibodies with the relative affinities as instantly claimed and to adjust their relative concentrations in the assay dependent upon the level of expected interfering material and its cross-reactivity with the cyclosporin specific antibody as taught in the reference. Further, the Patent and Trademark Office does not have the facilities and resources to provide the *factual* evidence needed in order to establish that there is a difference, in the first place, between the reagents of the prior art and those instantly disclosed and, that if there is such a difference, that such a difference would have been considered unexpected, i.e. unobvious, by one of ordinary skill in the art. The burden is upon applicant to present such factual evidence. See e.g. In re Best (195 USPQ 430 (CCPA 1977)) or Ex parte Phillips (28 USPQ2d 1302 (BPAI 1993)).

Claims 1-4, 6-11, 13, 14, and 16 are rejected under 35 U.S.C. § 102(b) as anticipated by or, in the alternative, under 35 U.S.C. § 103(a) as obvious over Halleen et al. (US 6,248,544).

Halleen et al. teach assays for the 5a and 5b isoforms of tartrate resistant acid phosphatase using two antibodies, one specific for the 5a form and one which binds to both the 5a and 5b forms. The antibodies are immobilized on solid phases and sequentially reacted with sample to bind the 5a form to the 5a-specific antibody and then the unbound 5b form to the tartrate resistant acid phosphatase-specific antibody. Bound enzymes are then detected by enzymatic assays performed at different pH values (see e.g. cols. 6-9). However, the relative affinities of the two antibodies for the two enzyme isoforms cannot be determined from the reference. Inherently the antibodies had the relative affinities as instantly claimed, or, in the alternative, it would have been obvious to have provided antibodies with the relative affinities as instantly claimed and to adjust their relative concentrations in the assay dependent upon the levels of expected isoforms. Moreover, it has been held that where the general conditions of a claim are disclosed in the prior art, discovering the optimum or workable ranges involves only routine skill in the art. *In re Aller*, 105 USPQ 233. Further, the Patent and Trademark Office does not have the facilities and resources to provide the *factual* evidence needed in order to establish that there is a difference, in the first place, between the reagents of the prior art and those instantly disclosed and, that if there is such a difference, that such a difference would have been considered unexpected, i.e. unobvious, by one of ordinary skill in the art. The burden is upon applicant to present such factual evidence. See e.g. In re Best (195 USPQ 430 (CCPA 1977)) or Ex parte Phillips (28 USPQ2d 1302 (BPAI 1993)).

Claims 1-4, 6-11, 13, 14, and 16 are rejected under 35 U.S.C. § 103(a) as being unpatentable over Halleen et al. (US 6,248,544) in view of Carlsson et al. (US 6,737,278).

The teachings of Halleen et al. (US 6,248,544) are as set forth above and differ from the invention as implied in the claims as not teaching a single solid phase for immobilization of the two antibodies.

Carlsson et al. teach a method and kit for performance of immunoassays on a flow matrix in which a separation zone is used between a sample application zone and an analyte detection zone for a variety of purposes, such as the binding of a heteroform of a protein in the separation zone to detect another heteroform in the detection zone, detecting active and inactive enzyme forms, or detecting degradation isoforms of proteins such as enzymes (see e.g. cols. 9-10). Direct detection of an enzyme analyte by incubation of bound enzyme with substrate is taught (see e.g. col. 11).

It would have been obvious to one of ordinary skill in the art at the time the instant invention was made to have used the flow matrix method and kit of Carlsson et al. for the determinations of the isoforms of tartrate resistant acid phosphatase in Halleen et al. in view of the direct suggestion in Carlsson et al. to use the method and kit for determinations of heteroforms having or lacking a binding site for a particular monoclonal antibody. One would have had an extremely reasonable expectation of success using the reagents and methods of Halleen et al. with such a matrix as taught in Carlsson et al. in view of the function of the reagents and methods for the determinations of the isoforms of tartrate resistant acid phosphatase taught in Halleen et al. and the direct suggestion for direct detection of bound enzymes with the flow matrix method and kit taught in Carlsson et al.

Thus, the claimed invention as a whole was clearly prima facie obvious, especially in the absence of evidence to the contrary.

The prior art made of record and not relied upon is considered pertinent to applicant's disclosure.

Ekins et al. (US 4,745,072) and Romelli et al. (US 5,382,530) teach the use of two antibodies specific for analyte and/or labeled analyte analogue in competitive assays for determination of analyte.

Ollington et al. (US 6,010,866) teach methods and devices for determination of analytes in samples containing interfering substances, such as determination of a particular acid phosphatase isozyme.

Ohashi et al. (US 7,074,903) teach the Trk49 and Trk62 antibodies.

Halleen et al. (J. Bone Mineral Res. 13: 683, 1998) teach sandwich immunoassays for the detection of intact tartrate resistant acid phosphatase and that high levels of tartrate resistant acid phosphatase fragments may be present in the circulation (see e.g. page 686).

Janckila et al. (Hybridoma 16: 175, 1997) teach a monoclonal antibody specific for denatured fragments of tartrate resistant acid phosphatase and not for active enzyme.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to James L. Grun, Ph.D., whose telephone number is (571) 272-0821. The examiner can normally be reached on weekdays from 9 a.m. to 5 p.m.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Long Le, SPE, can be contacted at (571) 272-0823.

The phone number for official facsimile transmitted communications to TC 1600, Group 1640, is (571) 273-8300.

Any inquiry of a general nature or relating to the status of this application, or requests to supply missing elements from Office communications, should be directed to the Group receptionist whose telephone number is (571) 272-1600.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

/JLG/
James L. Grun, Ph.D.
January 28, 2008

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